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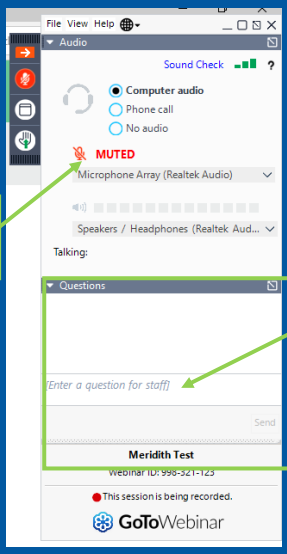
Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.



Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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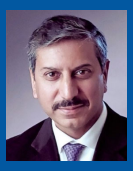
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

There will be no ACG Virtual Grand Rounds October 20th or 27th. Join us in Charlotte, NC for ACG 2022 – Annual Scientific Meeting & Postgraduate Course – October 21 – 26, 2022

Week 44 –Thursday, November 3, 2022
Obscure Bleeding: Are There Options After Endoscopy?
Faculty: Kathy P. Bull-Henry, MD, MBA, FACG
Moderator: John R. Saltzman, MD, FACG
Thursday, DATE at Noon Eastern and NEW! **8pm Eastern!**

Week 45 – Thursday, November 10, 2022
GI Diseases and Endoscopy in Pregnancy and Postpartum Period: The ACG Pregnancy Monograph
Faculty: Sunanda V. Kane, MD, MSPH, FACG
Moderators: Vivek Kaul, MD, FACG; and Shivangi T. Kothari, MD, FACG
Thursday, DATE at Noon Eastern and NEW! **8pm Eastern!**



Visit **gi.org/ACGVGR** to Register

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Disclosures

Monika Fischer, MD, MS, FACG
Rebiotix / Ferring: Advisor and Review Panel Member

Colleen R. Kelly, MD, FACG
Finch: Site for clinical trials
Sebela Pharmaceuticals: Consultant
Seres: Site for clinical trials

**All of the relevant financial relationships listed for these individuals have been mitigated*

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C. difficile Infection Treatment: What Is New?

Professor of Medicine
Indiana University School of Medicine
Indianapolis, IN

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Learning Objectives

- Goals of treatment of *C. difficile* infection
- New guideline recommendation for the treatment and prevention
  - Antibiotics, microbiome restoration, anti-toxin antibody
- Current indication of FMT in clinical practice
- Availability of FMT and how to refer for FMT?
- How to monitor patient post-FMT?
  - safety outcomes
  - prevention of reinfection
- What to do when FMT fails?
- Role of probiotics?
- What to do with the PPI?
- What's on the horizon in microbiome restoration therapy?

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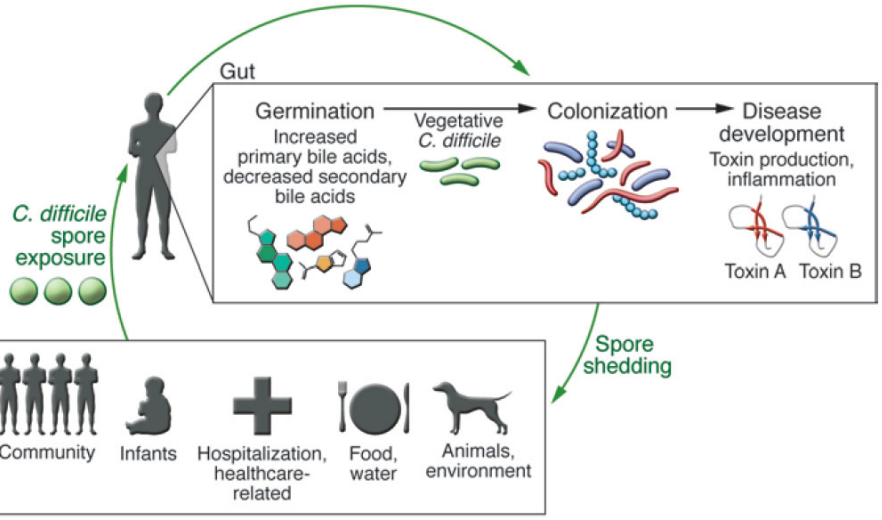
Clostridioides difficile Lifecycle



Seekatz AM, Young VB. J Clin Invest. 2014;124:4182-4189

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Goals of Treatment for *C difficile* Infection

Fidaxomicin
Vancomycin
Metronidazole

Vegetative Phase

Spore Phase

Healthy Diverse Microbiota

Kelly CR, et al. Amer J Gastro. 2021;116:1124-1147.

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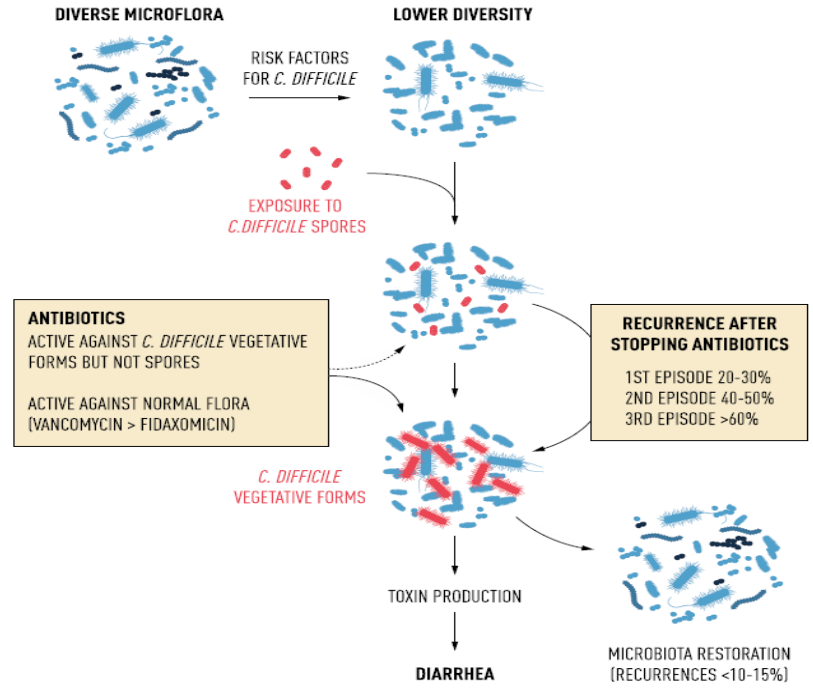
Microbiota restoration is the cornerstone of the management of recurrent *C difficile*



Khanna S. J Intern Med. 2021;290:294-309.

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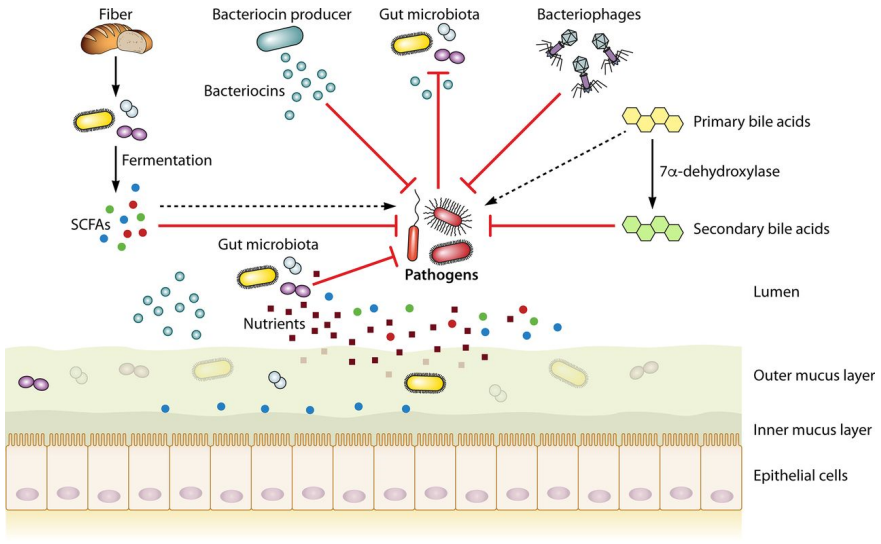
Microbiota-Mediated Colonization Resistance



Ducarmon QR, et al. Microbiol Mole Biol Rev. 2019;83:e00007-19. doi: 10.1128/MMBR.00007-19

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Treatment of Initial *C difficile* Infection

- **Bezlotoxumab for Prevention of CDI Recurrence in Patients With High Risk of Recurrence**

ACG | IDSA Infectious Diseases Society of America | ESCMID

Vancomycin or fidaxomicin	Fidaxomicin preferred over vancomycin	Fidaxomicin* preferred over vancomycin
Metronidazole alternate in low-risk	Metronidazole if above are unavailable	Metronidazole if above are unavailable

*High risk of recurrence: Age > 65 years + one or more of: healthcare-associated CDI, hospitalization in the last 3 months, concomitant non-CDI antibiotic use, PPI therapy and prior CDI

PPI, proton pump inhibitor

Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147; Johnson S, et al. Clin Infect Dis 2021:73:e1029-1044; Van Prehn J, et al. Clin Microbiol Infect. 2021;7:S1-S21.

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TREATMENT SHOULD BE BASED ON CDI SEVERITY AND PATIENT'S CIRCUMSTANCES

First line therapy: Antibiotics

$12 for 10 d course

$78-169 for 10 d course

$4,100 for 10 d course

Good Rx 8/30/21

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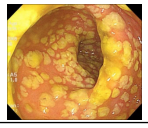
CLASSIFICATION OF CDI SEVERITY

Classification	Definition
Non-severe	Leukocytosis with a WBC <15,000 cells/mL and a serum creatinine level ≤1.5 mg/dL
Severe 	Leukocytosis with a WBC ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL
Fulminant	Criteria for severe infection, plus hypotension or shock, ileus, or megacolon

Kelly CR, et al. Amer J Gastro. 2021;116:1124-1147. Johnson S, et al. Clin Infect Dis 2021:73:e1029-1044

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Treatment of First Recurrence

ACG	IDSA Infectious Diseases Society of Americ	ESCMID
Fidaxomicin or vancomycin taper-pulse	Fidaxomicin* preferred over vancomycin taper-pulse	Fidaxomicin* preferred over vancomycin taper-pulse

- **Bezlotoxumab for Prevention of CDI Recurrence**

*Consider extended fidaxomicin regimen

Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147; Johnson S, et al. Clin Infect Dis 2021:73:e1029-1044; Van Prehn J, et al. Clin Microbiol Infect. 2021;7:S1-S21.

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Treatment of Multiply Recurrent *C difficile* Infection
≥ 2 recurrences or 3 episodes

ACG	IDSA Infectious Diseases Society of America	ESCMID
Abx ⟶ FMT Over antibiotic regimens	Abx ⟶ FMT Over antibiotic regimens	Abx ⟶ FMT Over antibiotic regimens

Consider Bezlotoxumab for prevention of CDI recurrence (If no FMT)

Kelly C, et al Am J Gastro 116(6):1124-1147; Johnson S, et al. Clin Infect Dis 2021:73:e1029-1044; van Prehn J, Clin Micro Inf Oct 2021

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Fecal microbiota transplantation

- Instillation of minimally manipulated microbial communities from stool of a healthy donor into a patient's GI tract
- FMT is distinguished from a defined consortia of microorganisms, highlighting the degree of complexity and functionality of the microbiome
- Considered both a "drug" and a "biologic or tissue" by the FDA

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Regulations: United States

- May use to treat *C. difficile* not responding to standard therapy
- No IND required
- Informed consent
  - State it is investigational
  - Discuss real and theoretical risks
- Draft guidance March 2016
  - Would enforce IND requirement for stool banks

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FMT and COVID-19

- Initially, material produced after Dec 1st 2019 was not eligible for use per FDA
- Openbiome and other stool banks have implemented Sars-Cov-2 screening in asymptomatic donors with NP swabs
- Stool testing is now being implemented for all banked samples
- No reports of transmission of Sars-Cov-2 via FMT to date
- FMT is currently sourced from Openbiome and mostly administered in clinical trials

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ACG 2021Guidelines recommendation regarding use of FMT in CDI

We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences

(Strong recommendation, moderate quality of evidence)

We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT

(Conditional recommendation, very low quality of evidence)

We suggest FMT be considered for patients with severe or fulminant CDI refractory to antimicrobial therapy, particularly, when patients are deemed poor surgical candidates

(Strong recommendation, low quality of evidence)

- Kelly CR, et al. Am J Gastroenterol. 2021;116:1124-1147.

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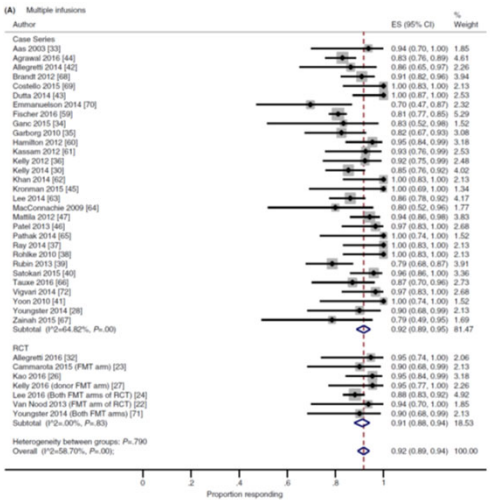
FMT Efficacy Meta-Analysis



- 37 studies
  - 7 RCT
  - 30 Case series
- FMT overall effectiveness of 92%
- FMT more effective than Vancomycin taper for recurrent/refractory CDI
- Lower administration more effective than upper administration
- No difference between fresh and frozen FMT

Quraishi et al. *Alim Pharm & Ther*. Sep;46(5):479-493. 2017

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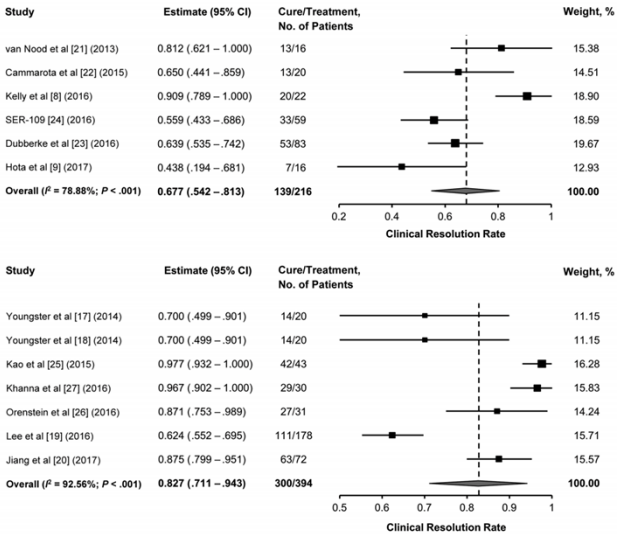
Lower Efficacy in RCTs vs Observational Studies



RCTs ~ 67% cure rate

Observational studies ~ 82% cure rate

Tariq R, et al. Clin Inf Dis. 2019. 68:1351-1358.

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Referral for FMT

Step 1:
Start an antibiotic to bring active symptoms under control

- Diarrhea improves in 3 to 5 days but risk of recurrence after 3 episodes is ~ 60%

Step 2:
Discuss recurrence prevention: Restore microbiome

- Initiate referral to a center / specialist performing microbiome restoration
  - Fecal microbiota transplantation
  - Clinical trials of microbiome restoration therapies
- Majority of patients will be discharged prior to getting microbiome restoration

Step 3:
Prescribe enough antibiotic until specialist appointment

- Vancomycin or fidaxomicin for 10 to 14 days
- Taper down antibiotics to lowest effective dose either once a day or once every other day

Voth E, et al. Expert Rev Anti Infect Ther. 2020;18:669-676.

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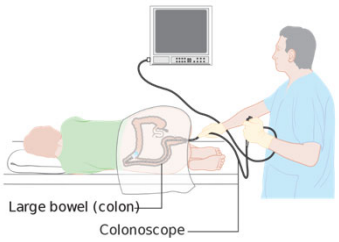
FMT Mode of Delivery

- Colonoscopy:
  - preferred in younger patients
  - unclear risk factors for CDI, can rule out IBD
  - upper GI dysfunction, dysmotility
  - Fulminant infection, ileus
- Capsules:
  - Preferred in most patients
  - Ease of administration
  - No sedation/procedure related complication
  - No bowel prep needed
  - More cost effective
- Enema: If other methods are unavailable



2021 ACG Guidelines

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Guideline Recommendations for Fulminant CDI

Guideline	Recommended Treatment
ACG	Multidisciplinary approach with surgical consultation Vancomycin 500 mg orally every 6 hours for first 48-72 hours Combination therapy with parenteral metronidazole 500 mg every 8 hours ***With Ileus:*** Addition of vancomycin enemas (500 mg every 6 hours) may be beneficial Consider IV tigecycline and FMT when refractory
ESCMID	Multidisciplinary approach with surgical consultation Vancomycin or fidaxomicin Consider IV tigecycline and FMT when refractory
IDSA	Multidisciplinary approach with surgical consultation Vancomycin 500 mg 4 x daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg q 8 hours) administered together with oral or rectal vancomycin, particularly if ileus is present

Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147; Johnson S, et al. Clin Infect Dis 2021:73:e1029-1044; Van Prehn J, et al. Clin Microbiol Infect. 2021;7:S1-S21.

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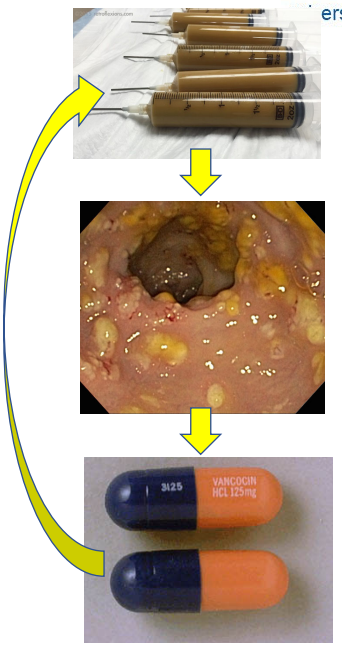
FMT for Severe and Fulminant CDI

- Consider for patients with severe and fulminant CDI refractory to antibiotics, particularly poor surgical candidates
  - Cure will likely require multiple FMTs + vancomycin or fidaxomicin
  - Pseudomembrane-driven FMT protocols



Fischer M. Aliment Pharm Thera 2015; Ianiro Aliment Pharmacol Thera 2018
Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147

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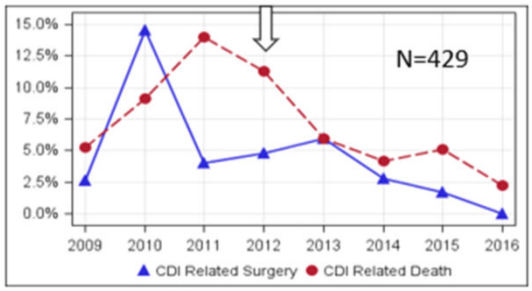
Inpatient FMT program decreases mortality and colectomy rate: IU experience



	Before FMT program	After FMT program	P-Value
CDI-Related Mortality, n (%)	21 (10.2%)	10 (4.5%)	0.021
CDI-Related Colectomy, n (%)	14 (6.8%)	6 (2.7%)	0.042

Pseudomembrane-driven FMT protocol for severe/fulminant CDI in the ICU, New York

A retrospective, matched cohort study of 48 patients

Outcomes	FMT	SOC	OR, 95% CI	P value
Death during admission (%)	3 (18.8%)	16 (50.0%)	0.23 (0.06-0.97)	.045
Colectomy during admission (%)	2 (12.5%)	3 (9.4%)	0.76 (0.11-5.08)	.77
Repeat CDI (%)[a]	3 (23.1%)	3 (18.8%)	1.30 (0.22-7.87)	.78
Readmission (%)[a]	8 (61.5%)	13 (81.3%)	0.37 (0.07-1.98)	.24

Cheng CGH 2020, Tixier Aliment.Pharmacol Ther 2019

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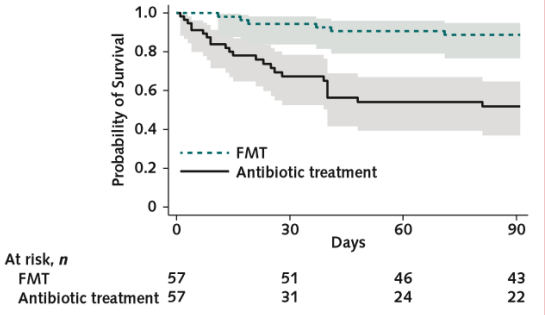
FMT decreases 90-day mortality and risk for blood stream infections in patients with CDI

Overall survival at 90 d in 57 patients treated with FMT compared with 57 patients treated with antibiotics matched by propensity score.



Shaded areas are 95% CIs. FMT = fecal microbiota transplantation.

	Treated With FMT	Treated With Antibiotics
Patients, *n*	57	57
Primary outcomes, *n* (%)		
BSI	2 (4)	15 (26)
Polymicrobial*	0 (0)	0 (0)
Bacterial	2 (4)	8 (14)
Fungal	0 (0)	7 (12)
Secondary outcomes		
Length of hospitalization	–	–
Mean (SD), *d*	13.4 (13.7)	27.8 (17.6)
Median (interquartile range), *d*	9 (2-21)	22 (14-40)
Overall survival at 90 d	–	–
Alive after 90 d, *n (%)*	51 (89)	33 (58)
Total deaths within 90 d, *n (%)*	6 (11)	22 (39)
Deaths in days 0-30, *n*	3	15
Deaths in days 31-90, *n*	3	7

Ianiro. Annals of Internal Medicine. 2019

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FMT in fulminant CDI

- No bowel prep in patients with ileus/toxic megacolon
- Banked FMT material helps with logistics
- Colonoscopy can be safely performed with CO2 insufflation
- Deliver FMT beyond splenic flexure
- May use vancomycin or fidaxomicin
- FMT can be repeated q 3-5 days depending on clinical course
- Finish protocol with FMT
- Ensure proper disinfection of patient room

Fischer Gut Microbes 2016, Cheng CGH 2020

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Adverse Events After Fecal Microbiota Transplant

- **Long-term effects of fecal transplant are unknown**

Transient constipation, diarrhea, discomfort	New medical conditions reported: single case reports	Infection transmission
▪ Post-infection irritable bowel syndrome	▪ Peripheral neuropathy ▪ Sjogren syndrome ▪ Idiopathic thrombocytopenic purpura ▪ Rheumatoid arthritis ▪ Obesity ▪ Microscopic colitis	▪ ESBL E coli ▪ Shiga toxin producing E coli

- ESBL, extended spectrum beta-lactamase.
- Brandt LJ, et al, Am J Gastroenterol. 2012;107:1079-87; Saha S, et al. Gastroenterology. 2021;160:1961-1969.e3.

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Long-term adverse events after multiply CDI and FMT

- **Reassuring data from national claims database**

- Retrospective cohort study using national commercial claims database
- Comparing outcomes of patients with non-mrCDI (N=124,068), mrCDI* (N=3692) without FMT and mrCDI with FMT (N=1165)
- Average follow-up: 2-2.5 years
- Relative to those with CDI, mrCDI and mrCDI with FMT was NOT associated with higher risk of HTN, DM, immune-mediated diseases or IBS
- Interestingly, FMT was associated with higher incidence of MI (aHR 1.68; 1.01-2.81) but not stroke; could not adjust for obesity or smoking

.Dawwas et al. CGH 2022 Apr;20(4):806-816.e6

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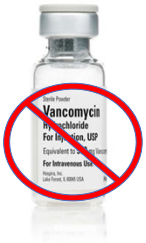
Patient discharge-education



1 Anti-*C.diff* antibiotic
- Do not continue

2 Do not "test for cure"
Diagnostic stewardship

3 Antibiotic stewardship
- Most vulnerable period: 8 weeks post FMT
- Prophylaxis: No role for probiotic or vancomycin

4 Home disinfection
- EPA approved sporicidal agents

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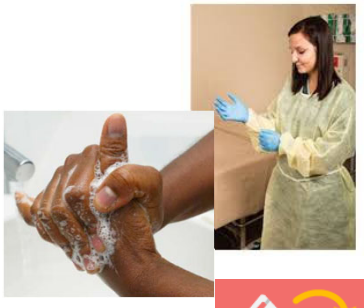
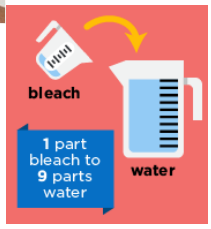
After FMT…
How to prevent C. diff reinfection?





- Spores can survive at room temperature up to 6 months and resistant to alcohol
- Use EPA approved sporicidal agents for home cleaning
- >40% of floors in commercial building, private homes, shoe soles are contaminated
- Wash hands with soap, clean with bleach, and take off your shoes!

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What to do if FMT fails 2x?

- Prefer colonoscopic delivery to rule out underlying pathology (IBD, microscopic colitis)
- Re-evaluate for causes
  - Repeated antibiotic use
  - Recurrent hospitalization
  - Improper home disinfection
  - Underlying IBD, immunodeficiency (CVID)
- Distinguish between infection and colonization
  - High incidence of post-infection IBS
- Repeat FMT, consider bidirectional FMT
- Consider long-term, low dose vancomycin prophylaxis

Testing outcome	
GDH- or PCR -	= negative
GDH+ EIA- PCR -	= nontoxigenic *C. diff*
GDH+ EIA+	= infection
GDH+ EIA- PCR+	= likely colonization

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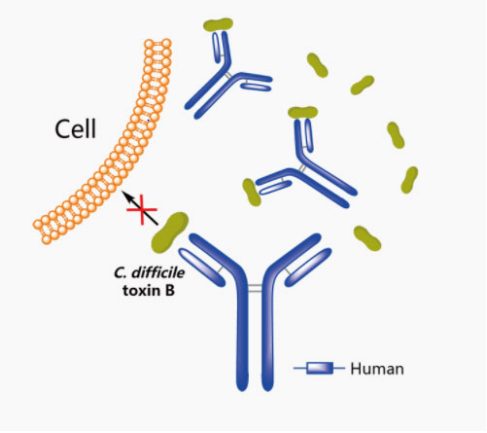
Immunotherapy: Bezlotoxumab

- IgG monoclonal antibody to toxin B
  - Single dose infusion 10mg/kg (~$4000)
  - MODIFY I/II: Recurrence: 16-17% vs 26-28% with placebo (NNT=10)
- Consider for prevention of CDI recurrence in patients who are at high risk of recurrence
- Recommended Patient Population: ≥ 65 years with at least one of these additional risk factors:
  - 2nd episode of CDI within the past 6 months
  - Immunocompromised
  - Severe CDI



Caution in patients with a history of heart failure or severe underlying cardiovascular comorbidities

Wilcox MC NEJM 2017

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No role for Probiotics in CDI

- PLACIDE Trial (Primary Prevention)
  - 2981 hospitalized, elderly patients in UK probiotics (4 strains) vs placebo
  - No difference in rate of AAD or CDI recurrence between groups
- Recent system-wide multicenter US study (Primary Prevention)
  - A 13 months long intervention of prescribing a 3-strain probiotic mixture (Bio-K+) to hospitalized patients age> 50 y on systemic antibiotics showed no impact in CDI incidence
- PICO Trial (Secondary Prevention)
  - Initial mild-to-moderate CDI on anti-CDI therapy randomized 33 patients to 4-strain probiotics or placebo. No difference in rates of CDI recurrence
- Not tightly regulated/Not risk free
  - Infections in immunocompromised patients
  - May impede normal recolonization after antibiotics
  - Expensive
- **ACG 2021 guidelines: "Recommend AGAINST the use of probiotics for both primary and secondary prevention of CDI".**
- **AGA 2020 guidelines: "In patients with *C difficile* infection, we recommend the use of probiotics only in the context of a clinical trial."**

ACG 2021 Guidelines. Kelly C, et al Am J Gastro 116(6):1124-1147. AGA guidelines on probiotics in GI disorder 2020. Su, G et al. Gastroenterology 2020;159:697–705

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Should PPI be discontinued?

- Do NOT recommend discontinuation, provided there is a valid indication for use
  - Assess patients for appropriateness of therapy and unnecessary PPIs should be discontinued
- Associations between PPI use and CDI in cohort studies (heterogeneity, unknown confounders, lack of dose-response relationships)
  - General population NNH (range, 899-3925)
  - Hospitalized patients not on antibiotics NNH (range, 202-367)
  - Hospitalized patients on antibiotics NNH (range, 28-50)
- Large RCT of 17,000 patients on ASA or rivaroxaban randomized to pantoprazole or placebo for 3 years did not show significant risk of CDI associated with PPI
  - 9 CDI in PPI group, 4 in control group (NS)*

Kelly C, et al Am J Gastro 116(6):1124-1147, *Moayyedi P Gastroenterol 2019

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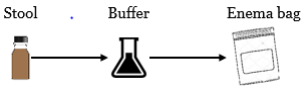
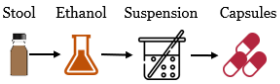
On the Horizon: Live Biotherapeutic Products (LBPs) in development for prevention of recurrence in multiply recurrent CDI

- RBX2660 (donor stool product, administered via enema)



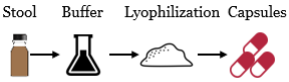
61-67%
(PUNCH-CD2)
70.4%
(PUNCH-CD3)

- SER-109 (isolated Firmicutes spores, encapsulated)



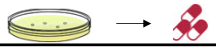
56%
(ECOSPOR)
87.6%
(ECOSPORE III)

- CP101 (full spectrum, lyophilized microbiota, encapsulated)



74.5%
(PRISM3)

- VE303 (8 clonal human commensal bacterial strains, encapsulated)



86.2%
(Phase 2)

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Take Home Points

- New guideline recommendation for CDI therapy
- Vancomycin and fidaxomicin equally recommended by ACG guidelines
- Metronidazole should be considered only for initial episode, non-severe infection, low risk patient
- FMT is the most effective therapy for recurrent disease
  - Consider for primary severe/refractory and fulminant CDI
- Only indication of FMT without an IND is “CDI not responding to standard of care antibiotic therapy”
- Refer to an FMT center, continue anti-CDI antibiotic therapy until appointment
- Post FMT follow up: infection control, minimize antibiotics, no role for probiotics, continue PPI if clinically indicated
- Consider bezlotoxumab for patients at high risk for recurrence and/or after FMT failure
- Near future: LBPs for prevention of recurrence

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Thank you

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Questions and Answers

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